CLINICAL STUDY

Variable growth hormone profiles following withdrawal of long-term 30 mg slow-release lanreotide treatment in acromegalic patients: clinical implications

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Abstract

Objective: Intramuscular injections of 30 mg slow-release (SR) lanreotide (every 10 to 14 days) are an effective treatment in acromegalic patients. Because of an ongoing need to assess the efficacy and the tolerance of a new formulation of a depot preparation of lanreotide, we have evaluated prospectively GH profiles following withdrawal of 30 mg slow-release lanreotide in a cohort of acromegalic patients. **Patients:** Fifty-one acromegalic patients, controlled during long-term 30 mg SR lanreotide treatment (GH: $1.44 \pm 0.64 \mu\text{g/l}$, IGF-I: $316 \pm 145 \text{ ng/ml}$) (mean $\pm$ s.d.), were studied following the withdrawal of the drug.

Measurements: Mean GH (half-hour samples, 0800–1200 h), IGF-I and lanreotide levels were evaluated 14, 28, and 42 days following the last 30 mg SR lanreotide injection.

Results: Mean GH levels remained below $2.5 \mu\text{g/l}$ in 32 patients (group 1) twenty-eight days following SR lanreotide withdrawal. In these patients, mean GH and IGF-I levels had increased from 1.2 ± 0.6 to $1.7 \pm 0.5 \mu\text{g/l}$ ($P < 0.001$), and from 283 ± 138 to $359 \pm 168 \text{ ng/ml}$ ($P < 0.001$) respectively. In the 19 other patients (group 2), mean GH concentrations had risen above $2.5 \mu\text{g/l}$ at 28 days following SR lanreotide withdrawal. Mean GH and IGF-I levels had increased from 1.9 ± 0.4 to $5.1 \pm 2.8 \mu\text{g/l}$ ($P < 0.001$), and from 371 ± 143 to $568 \pm 206 \text{ ng/ml}$ ($P < 0.001$) respectively. Patients of groups 1 and 2 were comparable with regard to age, sex, tumoral status, mean GH levels before somatostatin analogue treatment, and previous treatments such as radiotherapy and duration of somatostatin analogue therapy, but 75% of group 1 patients underwent surgery compared with 37% of group 2 patients ($P < 0.01$). Twenty-eight days following SR lanreotide withdrawal, mean lanreotide levels in group 1 and group 2 had decreased from 1.6 ± 0.7 to $0.6 \pm 0.3 \text{ ng/ml}$ ($P < 0.001$), and from 2.7 ± 2.0 to $0.7 \pm 0.7 \text{ ng/ml}$ ($P < 0.001$) respectively. A negative correlation was observed between the lanreotide levels and GH and IGF-I concentrations in the two groups of patients, but the inhibition of GH/IGF-I concentrations by lanreotide levels was higher in group 1 patients than in those of group 2. Six patients of group 1 were treated with 30 mg SR lanreotide injected at monthly intervals. During monthly follow-up, mean GH levels increased above $2.5 \mu\text{g/l}$ in 2 patients. After 12 months follow-up, mean GH and IGF-I levels from 4 other patients were similar to those obtained with previous therapeutic sequence (i.e. intramuscular injections every 14 days).

Conclusion: The degree of responsiveness to lanreotide and the duration of somatotroph suppression following lanreotide withdrawal are variable in acromegalic patients controlled during long-term 30 mg SR lanreotide treatment. In patients displaying high sensitivity to lanreotide, the interval between i.m. 30 mg SR lanreotide injections can be increased to one month, thus reducing the cost of the therapy, without altering its efficacy upon GH/IGF-I control.

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Introduction

The presence of somatostatin receptors in growth hormone (GH)-producing pituitary tumours has allowed consideration of treatment with somatostatin analogues in acromegaly. The effects of somatostatin analogue

treatments in acromegalic patients have been shown to be variable and reversible. In a previous multicentre study, normalization of plasma GH levels was obtained with octreotide treatment in 22% of the cases, whereas 56% of the patients exhibited partial inhibition of GH hypersecretion, and the treatment was ineffective in

22% (1). A shrinkage of somatotrophic adenomas was obtained in a subset of acromegalic patients (2). In the majority of the patients responding to somatostatin analogues, suppression of GH and insulin-like growth factor-I (IGF-I) levels by long-term subcutaneous octreotide or intramuscular lanreotide treatment did not persist after drug withdrawal, even after several years of administration (3–5). Today, long-acting somatostatin analogues are proposed as a definitive treatment for patients unwilling to undergo surgery or presenting with invasive macroadenomas in whom surgery may be hazardous or inadequate (6, 7). On the other hand, transient somatostatin analogue treatment can be indicated in order to reduce pituitary adenoma volume before surgery (8–10) or in the interim period until radiotherapy becomes fully effective.

In order to assess the efficacy and the safety of a new formulation of slow release (SR) lanreotide, we selected a cohort of 51 acromegalic patients considered as controlled during long-term 30 mg SR lanreotide treatment (i.e. mean GH level $< 2.5 \mu\text{g/l}$) (11–13). The aim of this study was to evaluate prospectively GH, IGF-I and lanreotide profiles following 30 mg SR lanreotide withdrawal in this large cohort of acromegalic patients.

Subjects and methods

Patients

The 51 acromegalic patients included in this multi-centre study were 30 women and 21 men, aged 56 ± 11 years (mean $\pm$ s.d.) (range 25–73 years). On computed tomography (CT) scan or nuclear magnetic resonance imaging (MRI), 12 of these patients had a macroadenoma with suprasellar extension and 36 had an intrasellar microadenoma or a postoperative intrasellar tumour residue. In 3 patients, radiological examination of the pituitary was normal. Incomplete surgical resection of the pituitary tumour ($n = 31$) and external radiation ($n = 18$) had been performed at least one year before the present study. Despite such treatments, the mean GH concentration was $13.6 \pm 19.9 \mu\text{g/l}$ (1.3 – $115 \mu\text{g/l}$) at the start of somatostatin analogue therapy. All patients were treated with 30 mg SR lanreotide i.m. every 10 ($n = 20$) to 14 days ($n = 31$) for a mean duration of 38 ± 28 months (1–113 months).

Study protocol

The present study was approved by the institutional ethics committee of the University of Aix-Marseille (France), and all patients gave written informed consent. We selected acromegalic patients considered to be well controlled during somatostatin analogue therapy, as their mean plasma GH level was less than $2.5 \mu\text{g/l}$, 10–14 days after an i.m. injection of 30 mg SR lanreotide. Blood for all measurements of GH concentrations was withdrawn every half-hour for 4 h

(between 0800–1200 h), 14, 28 and 42 days following SR lanreotide withdrawal. Plasma IGF-I and lanreotide levels were also determined 14, 28, and 42 days following withdrawal of SR lanreotide therapy. When GH levels remained below $2.5 \mu\text{g/l}$, mean GH and IGF-I levels were also evaluated at day 56.

Six patients in group 1 (5 women and 1 man, mean age 55 ± 9 years, range 44–65 years), previously treated with one injection every 14 days were subsequently treated with 30 mg SR lanreotide injected at monthly intervals, as their mean GH levels had increased above $2.5 \mu\text{g/l}$ ($3.3 \pm 0.7 \mu\text{g/l}$) (range 2.2– $3.8 \mu\text{g/l}$) at day 42 following 30 mg SR lanreotide withdrawal. Mean GH, IGF-I and lanreotide levels were evaluated after 1, 3, 6 and 12 months of such therapeutic sequence.

Hormone assays

Plasma GH concentrations were measured using a commercial assay kit (Cis Bio Elsa-HGH, Cis Bioindustries, Gif sur Yvette, France). The sensitivity of the GH assay was $0.04 \mu\text{g/l}$. The intra- and interassay coefficients of variation were 2.8% and 3.2% respectively. IGF-I levels were determined using a commercial immunoradiometric assay kit (IGF-I IRMA, Immunotech, Marseille, France) (14). The sensitivity of the IGF-I assay was 12 ng/ml . The intra- and interassay coefficients of variation were 5.7% and 8.6% respectively. The concentration of lanreotide was analysed by a radio-immunoassay method: the detection limit was 0.08 ng/ml , and the intra- and interassay coefficients of variation were less than 5% and 13% respectively. All hormone and lanreotide assays were centralized.

Data analysis

Results are expressed as means $\pm$ s.d. Statistical analysis was performed with the computer program SAS Institute Inc. (15). Analysis of the statistical data was based on the Chi-squared test, the Fisher exact test, the Wilcoxon test, and Student's *t*-test. Data were considered statistically significant if $P < 0.05$.

Results

Changes in GH and IGF-I levels following 30 mg SR lanreotide withdrawal (Fig. 1)

During long-term SR lanreotide treatment of the 51 acromegalic patients, mean GH and IGF-I levels were $1.4 \pm 0.6 \mu\text{g/l}$ (0.1 – $2.4 \mu\text{g/l}$) and $316 \pm 145 \text{ ng/ml}$ (65 – 683 ng/ml), respectively, 10–14 days after the last 30 mg SR lanreotide injection. Serum GH concentrations were significantly correlated with IGF-I levels ($P < 0.001$). Twenty-eight days following lanreotide withdrawal, mean GH levels remained below $2.5 \mu\text{g/l}$ in 32 acromegalic patients (group 1). In these patients, mean

Figure 1 Changes in GH and IGF-I levels (means $\pm$ S.E.M.) following 30 mg SR lanreotide withdrawal in 2 groups of acromegalic patients well controlled during long-term SR lanreotide treatment (group 1 GH $< 2.5 \mu\text{g/l}$, group 2 GH $> 2.5 \mu\text{g/l}$ twenty-eight days after the last injection of 30 mg SR lanreotide). * $P < 0.001$.

GH and IGF-I had increased from $1.2 \pm 0.6 \mu\text{g/l}$ ($0.1\text{--}2.3 \mu\text{g/l}$) to $1.7 \pm 0.5 \mu\text{g/l}$ ($0.2\text{--}2.4 \mu\text{g/l}$) ($P < 0.001$), and from $283 \pm 138 \text{ ng/ml}$ ($65\text{--}683 \text{ ng/ml}$) to $359 \pm 168 \text{ ng/ml}$ ($71\text{--}698 \text{ ng/ml}$) ($P < 0.001$) respectively. Despite GH levels less than $2.5 \mu\text{g/l}$, a moderate increase in IGF-I levels occurred in 47% of the patients one month following lanreotide withdrawal. Forty-two days after the last 30 mg SR lanreotide injection, the mean GH and IGF-I levels of the patients increased to $2.8 \pm 1.2 \mu\text{g/l}$ ($1.1\text{--}5.4 \mu\text{g/l}$) and to $457 \pm 209 \text{ ng/ml}$ ($160\text{--}1023 \text{ ng/ml}$) respectively. Fifty-six days following lanreotide withdrawal, 8 patients remained with mean GH levels less than $2.5 \mu\text{g/l}$ (mean GH = $2.0 \pm 0.3 \mu\text{g/l}$, $1.4\text{--}2.5 \mu\text{g/l}$, mean IGF-I = $298 \pm 47 \text{ ng/ml}$, $230\text{--}349 \text{ ng/ml}$).

Mean GH concentration was raised above $2.5 \mu\text{g/l}$ in the 19 other patients (group 2), 28 days following lanreotide withdrawal. In these patients, the mean GH and IGF-I levels had increased from $1.9 \pm 0.4 \mu\text{g/l}$

Table 1 Clinical and endocrine characteristics of group 1 and group 2 patients with acromegaly, well controlled during 30 mg SR lanreotide treatment.

	Group 1	Group 2
Number	32	19
Age (years)	57 ± 10	54 ± 12
Sex (M/F)	13/19	8/11
Mean GH ($\mu\text{g/l}$) ^a	11.6 ± 15.3	16.8 ± 25.7
Tumoral status		
Microadenoma/empty sella	27	13
Macroadenoma	5	6
Previous treatment		
Surgery	24	7*
Radiotherapy	13	5
Somatostatin analogues		
Duration (months)	35 ± 28	44 ± 30
Lanreotide every 10 days	10	10
Lanreotide every 14 days	22	9

^a Evaluated before the beginning of somatostatin analogue therapy.

* $P < 0.01$.

($1.1\text{--}2.4 \mu\text{g/l}$) to $5.1 \pm 2.8 \mu\text{g/l}$ ($2.6\text{--}12.0 \mu\text{g/l}$) ($P < 0.001$), and from $371 \pm 143 \text{ ng/ml}$ ($123\text{--}603 \text{ ng/ml}$) to $568 \pm 206 \text{ ng/ml}$ ($209\text{--}945 \text{ ng/ml}$) ($P < 0.001$) respectively. Despite GH levels greater than $2.5 \mu\text{g/l}$, two patients had normal IGF-I concentrations one month after drug withdrawal. Forty-two days after the last 30 mg SR lanreotide injection, mean GH and IGF-I levels in group 2 patients increased to $5.9 \pm 2.9 \mu\text{g/l}$ ($2.9\text{--}12.0 \mu\text{g/l}$) and to $708 \pm 254 \text{ ng/ml}$ ($248\text{--}1139 \text{ ng/ml}$) respectively.

Patients in groups 1 and 2 were comparable with regard to age, sex, tumoral status, mean GH levels before the institution of somatostatin analogue treatment, and previous therapies (radiotherapy, duration of somatostatin analogue treatment), but group 1 patients underwent surgery more frequently than group 2 patients ($P < 0.01$) (Table 1).

Changes in lanreotide levels following 30 mg SR lanreotide withdrawal (Fig. 2)

During long-term SR lanreotide treatment of the 51 acromegalic patients, the mean lanreotide level was $2.0 \pm 1.5 \text{ ng/ml}$ ($0.7\text{--}6.4 \text{ ng/ml}$), 10–14 days after the last 30 mg SR lanreotide injection. Indeed, the mean lanreotide level was significantly higher in patients treated with 30 mg SR lanreotide every 10 days ($2.6 \pm 1.7 \text{ ng/ml}$, $0.9\text{--}7.6 \text{ ng/ml}$) than in those injected every 14 days ($1.7 \pm 1.2 \text{ ng/ml}$, $0.7\text{--}6.4 \text{ ng/ml}$) ($P < 0.02$). The mean lanreotide level measured 10–14 days following the last injection of 30 mg SR lanreotide was significantly higher in group 2 patients ($2.6 \pm 1.9 \text{ ng/ml}$, $0.8\text{--}7.6 \text{ ng/ml}$) than in group 1 patients ($1.5 \pm 0.7 \text{ ng/ml}$, $0.7\text{--}3.9 \text{ ng/ml}$) ($P < 0.01$). Twenty-eight days after SR lanreotide withdrawal,

Figure 2 Changes in lanreotide levels (means $\pm$ S.E.M.) following 30 mg SR lanreotide withdrawal in 2 groups of acromegalic patients well controlled during long-term SR lanreotide treatment (group 1 GH $< 2.5 \mu\text{g/l}$, group 2 GH $> 2.5 \mu\text{g/l}$ twenty-eight days after the last injection of 30 mg SR lanreotide). * $P < 0.01$.

mean lanreotide levels in patients in groups 1 and 2 had decreased to $0.6 \pm 0.3 \text{ ng/ml}$ ($0.1\text{--}1.3 \text{ ng/ml}$) ($P < 0.001$), and to $0.8 \pm 0.7 \text{ ng/ml}$ ($0.2\text{--}2.4 \text{ ng/ml}$) ($P < 0.001$) respectively. From days 28 to 42, the mean plasma lanreotide levels declined similarly in both groups of patients. Forty-two days after lanreotide withdrawal, the mean lanreotide levels were $0.2 \pm 0.2 \text{ ng/ml}$ ($0.1\text{--}0.8 \text{ ng/ml}$) and $0.3 \pm 0.2 \text{ ng/ml}$ ($0.1\text{--}0.6 \text{ ng/ml}$) in groups 1 and 2 respectively.

Correlations between lanreotide levels and GH or IGF-I concentrations following withdrawal of 30 mg SR lanreotide (Fig. 3)

The effects of lanreotide on GH and IGF-I levels were evaluated in groups 1 and 2 of acromegalic patients, following the last SR lanreotide injection. A negative correlation was observed between the lanreotide levels and GH (group 1 $r = -0.57$, $P < 0.01$; group 2 $r = -0.45$, $P < 0.01$) and IGF-I (group 1 $r = -0.43$, $P < 0.01$; group 2 $r = -0.32$, $P < 0.02$) concentrations in the two groups of patients. The inhibition of GH/IGF-I levels by lanreotide was higher in patients in group 1 compared with those in group 2, implying that group 1 patients were more sensitive to lanreotide than acromegalic patients of group 2.

Efficacy of monthly 30 mg SR lanreotide injections

Six patients, among those who presented with a persistent suppression of GH hypersecretion during the 28-day period following SR lanreotide withdrawal (mean GH level $< 2.5 \mu\text{g/l}$) were subsequently treated

Figure 3 Correlations between lanreotide levels and GH or IGF-I concentrations in the 2 groups of acromegalic patients (group 1, open circles; group 2, closed circles) evaluated 14, 28 and 42 days following 30 mg SR lanreotide withdrawal.

by one injection of the drug repeated monthly. During such a treatment, the plasma GH and IGF-I levels were measured the day before the subsequent injection after 1, 3, 6 and 12 months of treatment. Mean GH levels of 2 patients increased above $2.5 \mu\text{g/l}$ after 6 and 9 months respectively, and these patients were treated again with the conventional therapeutic sequence (one 30 mg SR lanreotide injection every 14 days). In the other 4 patients, mean GH and IGF-I levels during the 12-month treatment with monthly 30 mg SR lanreotide injections were similar to those obtained with the conventional regimen (i.e. intramuscular injection every 14 days) of 30 mg SR lanreotide treatment, while mean lanreotide levels remained below 1 ng/ml (Table 2).

Discussion

Somatostatin analogues are an alternative treatment to pituitary surgery and radiotherapy in acromegalic

Table 2 GH, IGF-I and lanreotide levels in four group 1 acromegalic patients during the classical regimen of 30 mg SR lanreotide treatment (i.m. injections every 14 days), during SR lanreotide withdrawal, and during 1 year of monthly 30 mg lanreotide treatment.

	30 mg SR lanreotide every 14 days			Withdrawal			30 mg SR lanreotide every month			
	Before	During		28 days	42 days	1 month	3 months	6 months	12 months	
GH ($\mu\text{g/l}$)	13.4 $\pm$ 8.5***	1.16 $\pm$ 0.20		1.68 $\pm$ 0.38**	3.32 $\pm$ 0.73***	2.86 $\pm$ 0.45**	2.34 $\pm$ 0.60*	2.16 $\pm$ 0.66	2.01 $\pm$ 0.72	
IGF-I (ng/ml)	467 $\pm$ 98***	258 $\pm$ 76		323 $\pm$ 97*	372 $\pm$ 93**	300 $\pm$ 98	285 $\pm$ 73	262 $\pm$ 83	213 $\pm$ 103	
Lanreotide (ng/ml)	nd	1.53 $\pm$ 0.65		0.72 $\pm$ 0.22	0.13 $\pm$ 0.04	1.06 $\pm$ 0.52	0.91 $\pm$ 0.20	0.79 $\pm$ 0.34	nd	

* $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$ versus classical regimen of 30 mg SR lanreotide. nd, not done.

patients. Such medical treatment might be a suitable primary therapeutic modality in patients with large or invasive tumours. Recently, Newman *et al.* (16) reported a 68% or 62% return to normal IGF-I levels with octreotide as either primary or secondary therapy, suggesting that, if the possibility of surgical cure was low, octreotide may be a reasonable primary therapeutic modality, provided that the tumour does not threaten vision or neurological function. In this large cohort of acromegalic patients, long-term treatment with 30 mg SR lanreotide maintained safe GH concentrations (less than 2.5 $\mu\text{g/l}$) more easily in patients previously treated by surgery than in untreated patients. Thus, initial pituitary surgery still appears to be the best option for many patients with GH-secreting pituitary adenomas.

The effects of somatostatin analogue treatment on GH and IGF-I levels are reversible: suppression of GH and IGF-I levels does not persist after withdrawal of subcutaneous octreotide administration by either daily multiple injections (3) or continuous infusion (4), attesting the absence of a tumoricidal effect of somatostatin analogue treatment in acromegalic patients (17). Thus, new formulations of long-acting somatostatin analogues have been developed to avoid the drawbacks of repeated daily injections or continuous infusion of octreotide. The suppressive effect of these new formulations of somatostatin analogues is also reversible. After treatment for 1–3 years with monthly i.m. injections of a depot preparation of octreotide (Sandostatin-LAR, Sandoz Pharma, Basel, Switzerland), a reappearance of GH hypersecretion has been observed after the last injection of Sandostatin-LAR (18). Similarly, a clinical study with the long-acting somatostatin analogue, lanreotide, showed that mean GH and IGF-I levels increased progressively after drug discontinuation (5). In this cohort of 51 acromegalic patients, controlled during long-term 30 mg SR lanreotide treatment, mean GH levels increased but remained below 2.5 $\mu\text{g/l}$ one month following SR lanreotide withdrawal in 32 (63%) patients (group 1). On the other hand, mean GH levels rose more rapidly and were above 2.5 $\mu\text{g/l}$ at day 28 following the last injection of SR lanreotide in the 19 (37%) other patients (group 2). No rebound of GH secretion was observed following SR lanreotide withdrawal, as reported after cessation of octreotide treatment (3, 19). Thus, the suppressive effect on somatotroph activity observed during chronic treatment with repeated intramuscular injections of 30 mg SR lanreotide is reversible, but the reappearance of GH hypersecretion is variable following lanreotide withdrawal.

The effectiveness of somatostatin analogue treatment in acromegalic patients has been reported to be correlated with the molecular characteristics of the somatotroph cells (17, 20–26) as well as the plasma

concentration of somatostatin analogues (1, 27). In several studies, control of GH hypersecretion in acromegalic patients who respond to somatostatin analogues has been improved by increasing the dose of octreotide (28), and by changing the modalities of octreotide administration (29–31). Accordingly, continuous subcutaneous infusion of octreotide achieves superior and more sustained control of GH hypersecretion than intermittent repeated subcutaneous injections (27–29). Likewise, recent studies with the long-acting somatostatin analogue, lanreotide, report a significant reduction in mean GH values by increasing the frequency of intramuscular 30 mg SR lanreotide injections (4, 32, 33). In this cohort of acromegalic patients, controlled during long-term SR lanreotide treatment, the mean lanreotide level measured 10–14 days following the last injection of 30 mg SR lanreotide was significantly higher ($P < 0.01$) in group 2 patients than in those of group 1. This was related to the difference in the regimen of SR lanreotide injections between the two groups: 53% of the patients in group 2 had 30 mg SR lanreotide injections every 10 days, whereas 69% of the patients in group 1 had lanreotide injections every 14 days. However, mean lanreotide levels decreased more rapidly in group 2 than in group 1 patients between 10–14 and 28 days following the last injection of 30 mg SR lanreotide, suggesting that the clearance rate of lanreotide might be different in the two groups of acromegalic patients. On the other hand, higher lanreotide levels in acromegalic patients in group 2 than in group 1, measured 10–14 days after the last 30 mg SR lanreotide injection, as well as different correlations between GH/IGF-I concentrations and lanreotide levels evaluated in the two groups of patients during the follow-up of SR lanreotide withdrawal, suggest that the group 1 patients are more sensitive to lanreotide than those of group 2. Such variable sensitivities of acromegalic patients to somatostatin agonists have been correlated with the number, distribution and activity of somatostatin receptor subtypes on GH adenoma (17, 20, 21), with the adenylate cyclase activity in somatotroph cells (22), and with the presence of GS alpha mutations in adenoma cells (22–25). Therefore, the degree of responsiveness to lanreotide is variable in acromegalic patients. This may explain, at least in part, the variable regimen of 30 mg SR lanreotide injections required to control GH hypersecretion.

An individual adjustment of the time interval between 30 mg SR lanreotide injections (every 10 days instead of 14 days) has been proposed in acromegalic patients considered as responders to somatostatin analogue therapy, in order to obtain a better control of GH hypersecretion (32–34). In this study, 6 patients of group 1 were treated with monthly 30 mg SR lanreotide injections when mean GH had increased above $2.5 \mu\text{g/l}$ at day 42 following withdrawal of conventional lanreotide treatment. Indeed, it has

been suggested that this minimally supraphysiological elevation of GH levels can result in deleterious consequences and require treatment (11–13). In 4 patients, biochemical control of GH hypersecretion observed during monthly 30 mg SR lanreotide injections was similar to that obtained with the conventional regimen (i.e. injections every 14 days), whereas mean lanreotide levels remained below 1 ng/ml (35). Therefore, in a subset of acromegalic patients displaying high sensitivity to lanreotide, the interval between intramuscular 30 mg SR lanreotide injections can be increased, as previously reported (36), without altering its efficacy upon GH/IGF-I control, resulting in a reduction in the cost of such medical treatment.

Finally, in acromegalic patients treated by radiotherapy, transient somatostatin analogue treatment might be proposed in the interim period until this therapy becomes fully effective (7). Among 8 patients in group 1 with mean GH levels less than $2.5 \mu\text{g/l}$ at day 56 following the last 30 mg SR lanreotide injection, 4 had previously been treated by external radiation. The persistent control of GH hypersecretion in these patients could be due to the appearance of complete efficacy after such therapy. Therefore, an evaluation of GH secretion might be sequentially performed, after somatostatin analogue withdrawal, in patients previously treated by conventional radiation, proton beam therapy, gamma knife excision, and/or pituitary surgery in order to validate a persistent GH hypersecretion.

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